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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,518	03/09/2001	Gary Van Nest	377882001100	9215

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,518	VAN NEST, GARY	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-16,18-25,27,28 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-16,18-25,27,28 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the "Response and Amendment..." (Paper No. 14) and "Declaration..." (Paper No. 15) filed 3 April 2003 in reply to the Non-Final Office Action mailed 24 December 2002 (Paper No. 12). Claims 1-35 were considered in Paper No. 12. Claims 7, 17, 26, 29-32, 34 and 35 were canceled and claims 1, 10, 20 and 33 were amended in Paper No. 14. Claims 1-6, 8-16, 18-25, 27, 28 and 33 are pending and under consideration.

Response to Amendment

Rejection of claims 7, 17, 26, 29-32, 34 and 35 is rendered moot by cancellation of the claims in Paper No. 14.

Claims 1-6, 8-16, 18-25, 27, 28 and 33 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record in Paper No. 12 and herein below in the "Response to Arguments".

The Declaration under 37 CFR 1.132 (Paper No. 15) is sufficient to overcome the rejection of claims 1-6, 8-16, 18-25, 27, 28 based upon lack of enablement for a method wherein a composition comprising an immunostimulatory sequence is administered systemically.

Response to Arguments

Claims 1-6, 8-16, 18-25, 27, 28 and 33 were rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of

reducing the severity of a symptom of herpes virus infection in any individual or mammal comprising administering any sequence comprising 5'-C,G-3' sequence. It was indicated that the specification is enabling only for a method of preventing symptoms of, reducing severity of or reducing recurrence of a symptom of herpes infection in mice and guinea pigs challenged with herpes virus, by administering the *phosphorothioate* polynucleotide comprising the immunostimulatory sequences set forth as SEQ ID NO:1 and 9 to said mice and guinea pigs at a dose sufficient to prevent, or reduce severity or recurrence of a symptom of herpes infection.

In response to the rejection, Applicant has amended the claims such that they are now limited to the method wherein the polynucleotide comprises a phosphate backbone modification and wherein the treated individual is a mammal. Upon further consideration, the teachings of the art and specification are adequately enabling for a polynucleotide comprising a phosphate backbone modification. However, the claims lack enablement for immunostimulatory sequences other than those set forth as SEQ ID NO: 1 and 9 to and mammals other than mice and guinea pigs.

Applicant asserts that the claims are fully enabled for all mammalian species. First Applicant cites teachings from Agrawal (2002) *Trends Mol. Med.* 8:114-121 which Applicant characterizes as indicating, "the 5'-C,G-3' dinucleotide is essential to immunostimulatory activity and that changes in the flanking sequences may or may not optimize activity of an immunostimulatory oligonucleotide" (Paper No. 14, page 7). Thus Applicant seems to be asserting that the presence of an unmethylated 5'-C,G-3' sequence is sufficient to elicit an immune response capable of preventing a symptom of herpes simplex virus infection in any mammal and the flanking sequence merely fine tunes the response. This argument has been fully

considered but is not found persuasive. It must be kept in mind that the instant claims are directed to a method and kit for preventing a symptom of herpes simplex virus infection, they are not directed merely to a method of stimulating an immune response. Therefore the enabling disclosure must teach how to elicit an immune response of sufficient degree to prevent a symptom of herpes simplex virus infection. Agrawal *et al.* characterizes the response of human immune cells to a CpG polynucleotide capable of efficiently activating the mouse immune system as poor (paragraph bridging pages 114 and 115). And, as pointed out in the previous Office Action, Hartmann *et al.* (2000) *J. Immunol.* 164:1617-1624 teach that findings obtained using ISS in mice could not be extended to humans.

> "Hartmann *et al.* teach, '[r]ecently, we found that phosphorothioate ODN with the purine-purine-CG-pyrimidine-pyrimidine formula that had been identified as the most stimulatory motif in mice show no or only weak activity in human immune cells' (final paragraph on page 1617) and conversely, '[t]he human stimulatory ODN…shows weaker activity in mice compared with the highly active murine CpG ODN…supporting the concept of species specificity of CpG DNA recognition by immune cells' (second paragraph on page 1622). Hartmann *et al.* also teach that the effectiveness of any given ISS is unpredictable even within closely related mammalian species. In the second paragraph on page 1622, Hartmann *et al.* teach, '[a]lthough ODN 2006 was active in vitro in all primates tested, other CpG ODN, such as ODN 2007, had relatively high activity in human immune cells but no or a weaker effect in chimpanzees and rhesus monkeys.'" (Paper No. 12, page 8; emphasis added).

Thus, Hartmann *et al.* teaches that CpG-containing oligonucleotides found to be effective stimulators of immune responses in one species of mammal have little or no effect in other species. In view of these teachings, the skilled artisan clearly would not expect that any given CpG-containing oligonucleotide would be capable of eliciting an immune response of sufficient degree to prevent a symptom of herpes simplex virus infection in any and all mammals. Therefore, the skilled artisan would have to engage in empirical experimentation to identify an oligonucleotide capable of preventing a symptom of herpes simplex virus infection in each species of mammal encompassed by the claims.

Applicant next argues that the amount of experimentation required to practice the invention in any mammal would not be undue. Applicant asserts, "in view of the specification and that known in the art, it is well within the ability of a skilled artisan to vary sequences flanking the 5'-C,G-3' dinucleotide, if necessary, to generate an optimally active sequence" (page 8). Applicant states that the specification provides methods for synthesis and testing of ISS-containing polynucleotides and working examples that exemplify ISS-containing polynucleotides with activity as claimed. Applicant cites statements from *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) which indicate that some experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. Applicant argues that polynucleotides containing immunostimulatory sequences were known in the art and the specification provides considerable guidance as to how to make ISS-containing polynucleotides for use in the invention and how to assess activity.

This argument is not found persuasive because it fails to take into account the breadth of the claims and the unpredictability of extending the teachings of the specification to all mammalian species. In *In re Wands*, the court states, "[t]he determination of what constitutes undue experimentation in a given case requires the application of standard reasonableness, having due regard for the nature of the invention and the state of the art" (at 1404). The class Mammalia includes approximately 5,000 species, and, as described above, even closely related species differ dramatically in their response to any given CpG-containing oligonucleotide. Although the relative level of skill in the art is high, as pointed out in the previous office action, the art is immature and the factors dictating efficacy of CpG-containing oligonucleotides in mammals are largely unknown. Therefore, in order to practice the claimed invention according to its full scope, the skilled artisan would have to identify, by blind trial and error experimentation, an immunostimulatory oligonucleotide capable of eliciting an immune response of sufficient magnitude to prevent a symptom of herpes virus infection in each of the approximately 5,000 species encompassed by the claim. Clearly, the amount of experimentation required is beyond what would be considered reasonable or routine in the art. Therefore, the claims stand rejected as lacking enablement for the full scope of the claimed subject matter.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
June 3, 2003